Audet 09/871974 Applicant

CL. 33 COMPOUND

Page 1

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FILE 'HCAPLUS' ENTERED AT 09:16:40 ON 03 AUG 2005 L1 1 US2002147136/PN

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FILE 'HCAPLUS' ENTERED AT 09:17:16 ON 03 AUG 2005 L2 TRA L1 1- RN : 103 TERMS

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=> d all l1

- L1 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
- AN 2002:778699 HCAPLUS
- DN 137:299916
- ED Entered STN: 11 Oct 2002
- TI Peptide-containing compounds for targeting cells expressing NP-1 receptor
- IN Von Wronski, Mathew A.; Marinelli, Edmund R.; Nunn, Adrian D.; Pillai, Radhakrishna; Ramalingam, Kondareddiar; Tweedle, Michael F.; Linder, Karen; Nanjappan, Palaniappa; Raju, Natarajan
- PA USA
- SO U.S. Pat. Appl. Publ., 85 pp., Cont.-in-part of U.S. Ser. No. 585,364. CODEN: USXXCO
- DT Patent
- LA English
- IC ICM A61K038-16 ICS A61K051-08

INCL 514008000

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1, 8, 34

FAN.CNT 2

PATENT NO. KIND DATE APPLICATION NO. DATE

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US 2001-871974
                                                                   20010604 <--
   US 2002147136
                         A1 ·
                                20021010
PΙ
PRAI US 2000-585364
                         A2
                                20000602
CLASS
 PATENT NO.
                CLASS PATENT FAMILY CLASSIFICATION CODES
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                       A61K038-16
US 2002147136
                ICM
                ICS
                       A61K051-08
                       514008000
                INCL
                       514/008.000; 514/021.000; 424/001.110
               NCL
US 2002147136
                ECLA
                       A61K047/48R2; A61K049/00P8; A61K049/22P8; A61K049/22P4;
                       A61K049/22P16; A61K051/08Z
    MARPAT 137:299916
OS
    The present invention provides compds. for targeting endothelial cells,
AB
     tumor cells or other cells that express the neuropilin-1 (NP-1) receptor,
     compns. containing the same and methods for their use. The compds. are of the
     formula A-L-B (A = a monomer, multimer or polymer of TKPPR or analog which
     specifically binds to NP-1 or cells expressing NP-1 with avidity equal or
     greater than TKPPR; L = a lipid or a non-lipid (e.g., polymer) linker; B =
     a substrate). Addnl., the present invention includes diagnostic,
     therapeutic and radiotherapeutic compns. useful for visualization, therapy
     or radiotherapy. For example, DPPE-glutaroyl-Gly-Thr-Lys-Pro-Pro-Arg-OH
     (DPPE-Glu-GTKPPR) was prepared and formulated into gas-filled microbubble
     compns. for ultrasonic echog. The bubbles bind to human aortic
     endothelial cells (HAEC) under flow. The number of bubbles bound may
     increase with time for several minutes at a given flow rate, up to a flow
     rate producing 1.53 dynes/cm2, while bubbles without the targeting moiety
     (DPPE-Glu-GTKPPR) may not bind. However, once bound under a lesser flow
     rate (e.g., 1.53 dynes/cm2), the shear stress on bubbles containing
     DPPE-Glu-GTKPPR may be increased to 6.1 dynes/cm2 without dislodging many
     of the bound bubbles.
     peptide neuropilin receptor endothelium tumor targeting; antitumor
     angiogenesis inhibitor peptide deriv prepn; gene therapy radiotherapy
     peptide deriv; ultrasound imaging endothelium neuropilin peptide
IT
     Fusion proteins (chimeric proteins)
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (KDR/Fc, binding to human aortic endothelial cells inhibition by;
        preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     Receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (NP-1 (neuropilin-1); preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
     Imaging agents
TТ
        (acoustic imaging contrast agents; preparation of peptide-containing compds. and
        compns. for targeting cells expressing neuropilin-1 receptor for
        diagnosis, imaging, and therapy)
ΙT
     Imaging
     Imaging agents
        (acoustic; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
TT
        (aorta, endothelium, binding to; preparation of peptide-containing compds. and
        compns. for targeting cells expressing neuropilin-1 receptor for
        diagnosis, imaging, and therapy)
IT
        (aortic, binding to; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Drug delivery systems
        (beads; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT Diagnosis
```

Diagnosis

```
(cancer; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
тт
     Nucleic acids
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (delivery of; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
     Angiogenesis
IT
        (detection; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
     Blood vessel
IT
        (endothelium; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
тт
     Tumor necrosis factors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (human aortic endothelial cells activated by; preparation of peptide-containing
        compds. and compns. for targeting cells expressing neuropilin-1
        receptor for diagnosis, imaging, and therapy)
     Drug delivery systems
IT
        (kits; preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     Drug delivery systems
        (liposomes; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT
     Fluorescent substances
        (markers; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT
     Radionuclides, biological studies
     RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);
     USES (Uses)
        (markers; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT
     Air
        (microbubbles containing; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Alkenes, biological studies
     Alkvnes
     Hydrocarbons, biological studies
     Perfluorocarbons
     Perfluorocarbons
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (microbubbles containing; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
TΤ
     Drug delivery systems
        (microbubbles; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Drug delivery systems
        (microparticles; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
TТ
     Drug delivery systems
        (microspheres, fluorescent, peptide-conjugated; preparation of
        peptide-containing compds. and compns. for targeting cells expressing
        neuropilin-1 receptor for diagnosis, imaging, and therapy)
TТ
     Peptides, preparation
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
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```
(oligopeptides; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Virus
        (particles; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
     Angiogenesis inhibitors
TΤ
    Drug delivery systems
     Drug screening
     Gene therapy
     Genetic vectors
     Human
     Imaging
     Imaging agents
     Radiopharmaceuticals
     Radiotherapy
     Reducing agents
     Sound and Ultrasound
     Viral vectors
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     Phospholipids, reactions
IT
     Polymers, reactions
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
ΙT
     Drug delivery systems
        (suspensions, gas-filled microbubbles containing; preparation of peptide-containing
        compds. and compns. for targeting cells expressing neuropilin-1
        receptor for diagnosis, imaging, and therapy)
     Vascular endothelial growth factor receptors
TΤ
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (type VEGFR-2, activated, inhibition of; preparation of peptide-containing
        compds. and compns. for targeting cells expressing neuropilin-1
        receptor for diagnosis, imaging, and therapy)
     Endothelium
IT
        (vascular; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
                          127464-60-2, Vascular endothelial growth factor
IT
     9063-57-4, Tuftsin
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (binding to human aortic endothelial cells inhibition by; preparation of
        peptide-containing compds. and compns. for targeting cells expressing
        neuropilin-1 receptor for diagnosis, imaging, and therapy)
     14133-76-7DP, Technetium 99, complexes with tetrapeptide conjugate,
IT
     biological studies 470463-90-2DP, technetium 99 complexes
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (metastable; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
     124-38-9, Carbon dioxide, biological studies
                                                     2551-62-4, Sulfur
                   7439-90-9, Krypton, biological studies 7440-37-1, Argon,
     hexafluoride
                                                                 7727-37-9,
                          7440-63-3, Xenon, biological studies
     biological studies
     Nitrogen, biological studies 7782-44-7, Oxygen, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microbubbles containing; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT · 214210-47-6, Neuropilin-1
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     377087-52-0P, BRU 305
     RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic
```

```
preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant
     or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
TT
     377087-53-1P, BRU 306
     RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);
     BIOL (Biological study); PREP (Preparation)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
                                                    377088-92-1P, BRU 337
IT
     377087-63-3P, BRU 317
                            377087-82-6P, BRU 239
                                                    468726-69-4P
                            377725-24-1P, BRU 326
     377088-93-2P, BRU 346
     468729-71-7P
                  470463-86-6P, BRU 292
                                          470463-90-2P, BRU 363
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
                                      1155-64-2 1663-39-4, tert-Butyl
IT
     100-46-9, Benzylamine, reactions
               4530-20-5, Boc-glycine
                                       5681-36-7,
     acrvlate
     Dipalmitoylphosphatidylethanolamine
                                          7672-27-7
                                                      15401-08-8
                                                                  29022-11-5.
                   33662-26-9 71989-26-9 71989-35-0
                                                          82911-69-1
     Fmoc-glycine
                                   120791-76-6
                                                 129223-22-9
                                                               166108-71-0
     106392-12-5, Poloxamer F 108
                                                            283176-26-1
                                198139-51-4
                                              251450-64-3
     167393-62-6
                  169543-81-1
     377087-81-5D, resin bound
                                377087-83-7D, resin-bound
                                                           470444-40-7, BRU
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     4246-51-9P, 4,7,10-Trioxa-1,13-tridecanediamine
                                                      128988-04-5P
TT
     150525-42-1P
                   377087-49-5P
                                  377087-50-8P
                                                 377087-57-5P
                                                                377087-58-6P
                   377087-60-0P
                                   377087-62-2P
                                                 377087-64-4P
                                                                 377087-65-5P
     377087-59-7P
                   377087-67-7P
                                  377087-69-9P
                                                 377087-70-2P
                                                                 377087-71-3P
     377087-66-6P
     377087-72-4P
                   377087-73-5P 377087-74-6P
                                                 377087-76-8P
                                                                 377087-77-9P
     377087-78-0P
                   377087-79-1P
                                   377087-80-4P
                                                 377088-94-3P
                                                                 468726-65-0P
                                                 468726-71-8P
                                                                 468726-73-0P
                                  468726-70-7P
                   468726-68-3P
     468726-66-1P
     468726-75-2DP, resin bound
                                 468726-77-4DP, resin-bound 468729-73-9P
                                                 470463-88-8P
     468729-75-1P
                   468729-78-4P 470463-87-7P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     41961-58-4P
     RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     10098-91-6, Yttrium 90, biological studies 13967-64-1, Dysprosium 165,
IT
     biological studies 13967-65-2, Holmium 166, biological studies
     13968-53-1, Ruthenium 103, biological studies
                                                    13981-25-4, Copper 64,
     biological studies
                         13982-36-0, Yttrium 88, biological studies
     14119-09-6, Gallium 67, biological studies
                                                 14265-75-9, Lutetium 177,
                        14378-26-8, Rhenium 188, biological studies
     biological studies
                                     14998-63-1, Rhenium 186, biological
     14913-89-4, biological studies
              15750-15-9, Indium 111, biological studies 15757-14-9, Gallium
     studies
                             15758-35-7, Ruthenium 97, biological studies
     68, biological studies
     15766-00-4, Samarium 153, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (preparation of radiolabeled peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     42074-68-0
                 468726-76-3
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (resin-bound; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
      imaging, and therapy)
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     ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
L4
     2003-800817 [75]
AN
CR
     2002-195523 [25]
DNC C2003-221021
     Composition used in targeting endothelial cells e.g. tumor cells comprises
     compounds containing monomers, multimers or polymers of
     L-arginine-L-threonyl-L-lysyl-L-prolyl-L-prolyl.
DC
     A96 B04 K08
     LINDER, K; MARINELLI, E R; NANJAPPAN, P; NUNN, A D; PILLAI, R; RAJU, N;
IN
     RAMALINGAM, K; TWEEDLE, M F; VON WRONSKI, M A
     (LIND-I) LINDER K; (MARI-I) MARINELLI E R; (NANJ-I) NANJAPPAN P; (NUNN-I)
     NUNN A D; (PILL-I) PILLAI R; (RAJU-I) RAJU N; (RAMA-I) RAMALINGAM K;
     (TWEE-I) TWEEDLE M F; (VWRO-I) VON WRONSKI M A
CYC
     US 2002147136 A1 20021010 (200375)*
                                                85
                                                      A61K038-16
ADT US 2002147136 A1 CIP of US 2000-585364 20000602, US 2001-871974 20010604
                                                          20000602
PRAI US 2001-871974
                          20010604; US 2000-585364
     ICM A61K038-16
     ICS A61K051-08
AB
     US2002147136 A UPAB: 20031120
     NOVELTY - Composition (A1) comprises compounds containing monomers,
     multimers or polymers of L-arginine-L-threonyl-L-lysyl-L-prolyl-L-prolyl.
          DETAILED DESCRIPTION - Composition (A1) comprises a compound
     containing monomers, multimers or polymers of L-arginine-L-threonyl-L-
     lysyl-L-prolyl-L-prolyl (TKPPR) of formula A-L-B1 (I).
          A = monomer, multimer or polymer of TKPPR or its analogue that
     specifically binds to NP-1 or cells that express NP-1 with avidity of at
     least that of TKPPR;
          L = a linker (preferably a group of formula (i));
          X = NH, NR, O, S or SR;
     m = 0-2;
```

n = 0-4;

R = H or 1-4C alkyl (optionally substituted by at least one OH), and

```
B1 = a substrate.
          INDEPENDENT CLAIMS are also included for:
          (1) a compound of formula A-L-Bla (II) and A-L-B3 (III) for use in
     targeting endothelial cells, tumor cells or other cells;
          (2) an ultrasound contrast agent (c1) comprising a suspension of gas
     filled microbubbles comprising (II);
          (3) an ultrasound contrast agent (c2) comprising a suspension of gas
     filled microballoons comprising (III);
          (4) preparation of (I) which comprises conjugating the monomer,
     multimer or polymer of TKPRR or its analogue with a linker to obtain a
     compound of formula A-L (IV), forming a covalent or non-covalent bond
     between (IV) and the substrate B1 or forming a covalent bond between B1
     and the linker to form a conjugate B-L followed by conjugation with the
     monomer, and
          (5) a kit for preparing a radiopharmaceutical comprising (A1).
          Bla = a phospholipid group of formula (ii);
          M = alkaline or alkaline earth metal cation;
          R1, R2 = 12-20C linear chain optionally interrupted by CO or O, and
          X2 = H, CH2CH2NH2, CH2CH(NH3+)-COO-, CH2CH(OH)CH2OH or a group of
     formula (iii).
          ACTIVITY - Cytostatic; Antiangiogenetic.
          MECHANISM OF ACTION - Vascular endothelial growth factor binding
     receptor transmembrane glycoprotein (NP-1) binder.
          USE - Used for targeting endothelial cells, tumor cells or other
     cells which express NP-1, for inhibiting angiogenesis, for ultrasound
     imaging, staging a tumor, screening at least one targeted ultrasound
     contrast agent for the ability to target endothelial cells, tumor cells or
     other cells which express NP-1, for the therapeutic delivery in vivo of a
     bioactive agent and for delivering desired nucleic acids to endothelial
     cells, tumor cells or other cells which express NP-1 (all claimed). The
     composition is also useful for visualization therapy or radiotherapy of
     endothelial cells.
          ADVANTAGE - (A1) can be used with or without a detectable moiety for
     any of the imaging modalities.
     Dwg.0/4
FS
     CPI
FA
     AB; GI; DCN
     CPI: A12-V01; A12-V03C2; B01-D02; B03-H; B04-B01B; B04-C01A; B04-C02;
          B04-C03; B04-D01; B04-J02; B05-A03B; B05-A04; B05-B01P; B05-B02C;
          B05-C08; B10-A07; B10-B02J; B10-B04B; B10-C02; B10-H02B; B12-K04C1;
          B14-F01D; B14-H01; K08-X; K09-B; K09-E
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         *32* DCN: 0097-34701-T; 0097-34701-M; 0097-34701-N
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         *41* DCN: RA01PM-K; RA01PM-T; RA01PM-Q; RA01PM-M
     M1
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         *43* DCN: RA0121-K; RA0121-T; RA0121-Q; RA0121-M
         *44* DCN: RA04V6-K; RA04V6-T; RA04V6-Q; RA04V6-M
         *45* DCN: RA0120-K; RA0120-T; RA0120-Q; RA0120-M
         *46* DCN: RAAXLX-K; RAAXLX-T; RAAXLX-Q; RAAXLX-M
         *47* DCN: 0097-34703-K; 0097-34703-T; 0097-34703-Q; 0097-34703-M;
                    0097-34703-P
         *01* DCN: RA04F6-K; RA04F6-T; RA04F6-Q; RA04F6-M
     M2
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*03* DCN: R07812-K; R07812-T; R07812-Q; R07812-M
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         *04* DCN: R09617-K; R09617-T; R09617-Q; R09617-M; R10728-K; R10728-T;
                    R10728-Q; R10728-M
         *05* DCN: R01065-K; R01065-T; R01065-Q; R01065-M
         *06* DCN: RA0ICL-K; RA0ICL-T; RA0ICL-Q; RA0ICL-M
*07* DCN: RA11FY-K; RA11FY-T; RA11FY-Q; RA11FY-M
         *08* DCN: RA1AGG-K; RA1AGG-T; RA1AGG-Q; RA1AGG-M
         *09* DCN: RA0K4Y-K; RA0K4Y-T; RA0K4Y-Q; RA0K4Y-M
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*10* DCN: R00104-K; R00104-T; R00104-Q; R00104-M; R04091-K; R04091-T;
                    R04091-Q; R04091-M; R13229-K; R13229-T; R13229-Q; R13229-M
         *11* DCN: R00116-K; R00116-T; R00116-Q; R00116-M; R04750-K; R04750-T;
                    R04750-Q; R04750-M
         *12* DCN: R00114-K; R00114-T; R00114-Q; R00114-M; R04738-K; R04738-T;
                    R04738-Q; R04738-M
         *13* DCN: R00100-K; R00100-T; R00100-Q; R00100-M; R17997-K; R17997-T;
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                    R17997-Q; R17997-M
         *14* DCN: R06639-K; R06639-T; R06639-Q; R06639-M
     M2
         *15* DCN: R00900-K; R00900-T; R00900-Q; R00900-M; R07861-K; R07861-T;
                    R07861-Q; R07861-M
         *16* DCN: R01137-K; R01137-T; R01137-Q; R01137-M; R12109-K; R12109-T;
                    R12109-Q; R12109-M
         *17* DCN: R01152-K; R01152-T; R01152-Q; R01152-M; R07021-K; R07021-T;
                    R07021-Q; R07021-M
         *18* DCN: R08480-K; R08480-T; R08480-Q; R08480-M
         *19* DCN: R10312-K; R10312-T; R10312-Q; R10312-M
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     M2
         *22* DCN: R16328-K; R16328-T; R16328-Q; R16328-M
     M2
         *23* DCN: R01738-K; R01738-T; R01738-Q; R01738-M
         *24* DCN: R01779-K; R01779-T; R01779-Q; R01779-M
         *25* DCN: R03186-K; R03186-T; R03186-Q; R03186-M
         *26* DCN: R03134-K; R03134-T; R03134-Q; R03134-M
*27* DCN: R03133-K; R03133-T; R03133-Q; R03133-M
     M2
         *28* DCN: RAOXPN-K; RAOXPN-T; RAOXPN-Q; RAOXPN-M
     M2
         *29* DCN: R18066-K; R18066-T; R18066-Q; R18066-M
     M2 *30* DCN: RAAXL7-K; RAAXL7-T; RAAXL7-Q; RAAXL7-M
     M5 *33* DCN: R11954-K; R11954-T; R11954-Q; R11954-M
        *34* DCN: R13257-K; R13257-T; R13257-Q; R13257-M
*35* DCN: R00148-K; R00148-T; R00148-Q; R00148-M
     M5 *36* DCN: RAAXKP-K; RAAXKP-T; RAAXKP-Q; RAAXKP-M
DRN 0100-S; 0100-U; 0104-S; 0104-U; 0114-S; 0114-U; 0116-S; 0116-U; 0148-S;
     0148-U; 0900-S; 0900-U; 1065-S; 1065-U; 1137-S; 1137-U; 1152-S; 1152-U;
     1738-S; 1738-U; 1779-S; 1779-U
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=> b home FILE 'HÓME' ENTERED AT 09:18:08 ON 03 AUG 2005

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=> b reg FILE 'REGISTRY' ENTERED AT 09:23:58 ON 03 AUG 2005 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2005 American Chemical Society (ACS)

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STRUCTURE FILE UPDATES: 2 AUG 2005 HIGHEST RN 857941-82-3 DICTIONARY FILE UPDATES: 2 AUG 2005 HIGHEST RN 857941-82-3

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at: http://www.cas.org/ONLINE/DBSS/registryss.html

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- L6 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN
- RN 468726-69-4 REGISTRY
- ED Entered STN: 01 Nov 2002
- CN L-Arginine, N-[(13R)-10-hydroxy-10-oxido-1,5,16-trioxo-13-[(1-oxohexadecyl)oxy]-9,11,15-trioxa-6-aza-10-phosphahentriacont-1-yl]glycyl-L-threonyl-L-lysyl-L-prolyl-L-prolyl- (9CI) (CA INDEX NAME)
- FS PROTEIN SEQUENCE; STEREOSEARCH
- MF C70 H128 N11 O18 P
- SR CA
- LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
- **RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.

PAGE 1-A

PAGE 1-B

PAGE 2-B

- 1 REFERENCES IN FILE CA (1907 TO DATE)
- 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)
- ANSWER 2 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN L6
- 377087-37-1 REGISTRY RN
- Entered STN: 20 Dec 2001 ED
- L-Arginine, N-[10-hydroxy-10-oxido-1,5,16-trioxo-13-[(1-oxohexadecyl)oxy]-CN9,11,15-trioxa-6-aza-10-phosphahentriacont-1-yl]glycyl-L-threonyl-L-lysyl-L-prolyl-L-prolyl- (9CI) (CA INDEX NAME)
- PROTEIN SEQUENCE; STEREOSEARCH FS MF C70 H128 N11 O18 P
- CA SR
- LC STN Files:
- CA, CAPLUS, TOXCENTER
- **RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.

PAGE 1-A

PAGE 1-B

· PAGE 2-A CO2H

PAGE 2-B



- 1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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(FILE 'HOME' ENTERED AT 09:16:15 ON 03 AUG 2005)

FILE 'HCAPLUS' ENTERED AT 09:16:40 ON 03 AUG 2005 L11 US2002147136/PN

FILE 'REGISTRY' ENTERED AT 09:17:15 ON 03 AUG 2005

FILE 'HCAPLUS' ENTERED AT 09:17:16 ON 03 AUG 2005 L2 TRA L1 1- RN : 103 TERMS

FILE 'REGISTRY' ENTERED AT 09:17:17 ON 03 AUG 2005 L3 103 SEA L2

FILE 'WPIX' ENTERED AT 09:17:21 ON 03 AUG 2005 L41 L1

FILE 'REGISTRY' ENTERED AT 09:18:43 ON 03 AUG 2005 3 L3 AND O>=18 AND P/ELS AND NC4/ES L5 L6 2 C70H128N11O18P FILE 'HCAPLUS' ENTERED AT 09:24:13 ON 03 AUG 2005 L7 FILE 'EMBASE' ENTERED AT 09:24:28 ON 03 AUG 2005 L8 FILE 'MEDLINE' ENTERED AT 09:24:37 ON 03 AUG 2005 0 L6 L9 FILE 'BIOSIS' ENTERED AT 09:24:42 ON 03 AUG 2005 L10 0 L6 FILE 'HCAOLD' ENTERED AT 09:24:47 ON 03 AUG 2005 0 L6 L11 FILE 'USPATFULL, USPAT2' ENTERED AT 09:25:03 ON 03 AUG 2005 L12 FILE 'WPIX' ENTERED AT 09:31:08 ON 03 AUG 2005 1 C70 H128 N11 O18 P/MF L13 SEL SDCN L13 1 E1/DCN L14 => b hcap

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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- L7 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
- AN 2002:778699 HCAPLUS
- DN 137:299916
- ED Entered STN: 11 Oct 2002
- TI Peptide-containing compounds for targeting cells expressing NP-1 receptor
- IN Von Wronski, Mathew A.; Marinelli, Edmund R.; Nunn, Adrian D.; Pillai, Radhakrishna; Ramalingam, Kondareddiar; Tweedle, Michael F.; Linder, Karen; Nanjappan, Palaniappa; Raju, Natarajan
- PA USA
- SO U.S. Pat. Appl. Publ., 85 pp., Cont.-in-part of U.S. Ser. No. 585,364. CODEN: USXXCO

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DT
    Patent
LΑ
    English
    ICM A61K038-16
IC
    ICS A61K051-08
INCL 514008000
    63-6 (Pharmaceuticals)
     Section cross-reference(s): 1, 8, 34
FAN.CNT 2
                                                                   DATE
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                                            APPLICATION NO.
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                                            US 2001-871974
                                                                   20010604
                                20021010
    US 2002147136
                         A1
PRAI US 2000-585364
                         A2
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CLASS
                CLASS PATENT FAMILY CLASSIFICATION CODES
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                       A61K051-08
                ICS
                INCL
                        514008000
                        514/008.000; 514/021.000; 424/001.110
                NCL
 US 2002147136
                       A61K047/48R2; A61K049/00P8; A61K049/22P8; A61K049/22P4;
                ECLA
                        A61K049/22P16; A61K051/08Z
OS
    MARPAT 137:299916
    The present invention provides compds. for targeting endothelial cells,
AB.
     tumor cells or other cells that express the neuropilin-1 (NP-1) receptor,
     compns. containing the same and methods for their use. The compds. are of the
     formula A-L-B (A = a monomer, multimer or polymer of TKPPR or analog which
     specifically binds to NP-1 or cells expressing NP-1 with avidity equal or
     greater than TKPPR; L = a lipid or a non-lipid (e.g., polymer) linker; B =
     a substrate). Addnl., the present invention includes diagnostic,
     therapeutic and radiotherapeutic compns. useful for visualization, therapy
     or radiotherapy. For example, DPPE-glutaroyl-Gly-Thr-Lys-Pro-Pro-Arg-OH
     (DPPE-Glu-GTKPPR) was prepared and formulated into gas-filled microbubble
     compns. for ultrasonic echoq. The bubbles bind to human aortic
     endothelial cells (HAEC) under flow. The number of bubbles bound may
     increase with time for several minutes at a given flow rate, up to a flow
     rate producing 1.53 dynes/cm2, while bubbles without the targeting moiety
     (DPPE-Glu-GTKPPR) may not bind. However, once bound under a lesser flow
     rate (e.g., 1.53 dynes/cm2), the shear stress on bubbles containing
     DPPE-Glu-GTKPPR may be increased to 6.1 dynes/cm2 without dislodging many
     of the bound bubbles.
     peptide neuropilin receptor endothelium tumor targeting; antitumor
ST
     angiogenesis inhibitor peptide deriv prepn; gene therapy radiotherapy
     peptide deriv; ultrasound imaging endothelium neuropilin peptide
     Fusion proteins (chimeric proteins)
TΤ
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (KDR/Fc, binding to human aortic endothelial cells inhibition by;
        preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis; imaging, and therapy)
TT
     Receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (NP-1 (neuropilin-1); preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Imaging agents
        (acoustic imaging contrast agents; preparation of peptide-containing compds. and
        compns. for targeting cells expressing neuropilin-1 receptor for
        diagnosis, imaging, and therapy)
IT
     Imaging
     Imaging agents
        (acoustic; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IΤ
     Artery
        (aorta, endothelium, binding to; preparation of peptide-containing compds. and
        compns. for targeting cells expressing neuropilin-1 receptor for
        diagnosis, imaging, and therapy)
```

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IT
     Endothelium
        (aortic, binding to; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
     Drug delivery systems
IT
        (beads; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT
     Diagnosis
     Diagnosis
        (cancer; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT
     Nucleic acids
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (delivery of; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
     Angiogenesis
IT
        (detection; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
IT
     Blood vessel
        (endothelium; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
     Tumor necrosis factors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (human aortic endothelial cells activated by; preparation of peptide-containing
        compds. and compns. for targeting cells expressing neuropilin-1
        receptor for diagnosis, imaging, and therapy)
ΙT
     Drug delivery systems
        (kits; preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     Drug delivery systems
        (liposomes; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
     Fluorescent substances
TT
        (markers; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
     Radionuclides, biological studies
IT
     RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);
     USES (Uses)
        (markers; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
IT
     Air
        (microbubbles containing; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
     Alkenes, biological studies
IT
     Alkynes
     Hydrocarbons, biological studies
     Perfluorocarbons
     Perfluorocarbons
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (microbubbles containing; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Drug delivery systems
        (microbubbles; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
```

Drug delivery systems

ΙT

```
(microparticles; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Drug delivery systems
        (microspheres, fluorescent, peptide-conjugated; preparation of
        peptide-containing compds. and compns. for targeting cells expressing
        neuropilin-1 receptor for diagnosis, imaging, and therapy)
     Peptides, preparation
TΤ
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (oligopeptides; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     Virus
        (particles; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
IT
     Angiogenesis inhibitors
     Drug delivery systems
    Drug screening
     Gene therapy
     Genetic vectors
     Human
     Imaging
     Imaging agents
     Radiopharmaceuticals
     Radiotherapy
     Reducing agents
     Sound and Ultrasound
     Viral vectors
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     Phospholipids, reactions
     Polymers, reactions
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     Drug delivery systems
        (suspensions, gas-filled microbubbles containing; preparation of peptide-containing
        compds. and compns. for targeting cells expressing neuropilin-1
        receptor for diagnosis, imaging, and therapy)
     Vascular endothelial growth factor receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (type VEGFR-2, activated, inhibition of; preparation of peptide-containing
        compds. and compns. for targeting cells expressing neuropilin-1
        receptor for diagnosis, imaging, and therapy)
IT
     Endothelium
        (vascular; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
                         127464-60-2, Vascular endothelial growth factor
     9063-57-4, Tuftsin
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (binding to human aortic endothelial cells inhibition by; preparation of
        peptide-containing compds. and compns. for targeting cells expressing
        neuropilin-1 receptor for diagnosis, imaging, and therapy)
TT
     14133-76-7DP, Technetium 99, complexes with tetrapeptide conjugate,
     biological studies 470463-90-2DP, technetium 99 complexes
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (metastable; preparation of peptide-containing compds. and compns. for targeting
        cells expressing neuropilin-1 receptor for diagnosis, imaging, and
        therapy)
     124-38-9, Carbon dioxide, biological studies 2551-62-4, Sulfur hexafluoride 7439-90-9, Krypton, biological studies 7440-37-1, Argon,
IT
     biological studies 7440-63-3, Xenon, biological studies 7727-37-9,
     Nitrogen, biological studies 7782-44-7, Oxygen, biological studies
```

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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (microbubbles containing; preparation of peptide-containing compds. and compns. for
        targeting cells expressing neuropilin-1 receptor for diagnosis,
        imaging, and therapy)
IT
     214210-47-6, Neuropilin-1
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     377087-52-0P, BRU 305
IT
     RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic
     preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant
     or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     377087-53-1P, BRU 306
TT
     RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);
     BIOL (Biological study); PREP (Preparation)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     377087-63-3P, BRU 317 377087-82-6P, BRU 239
                                                    377088-92-1P, BRU 337
IT
                            377725-24-1P, BRU 326 468726-69-4P
     377088-93-2P, BRU 346
                                            470463-90-2P, BRU 363
     468729-71-7P
                    470463-86-6P, BRU 292
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     100-46-9, Benzylamine, reactions 1155-64-2
                                                   1663-39-4, tert-Butyl
IT
               4530-20-5, Boc-glycine 5681-36-7,
     acrvlate
                                          7672-27-7
     Dipalmitoylphosphatidylethanolamine
                                                       15401-08-8
                                71989-26-9
                                              71989-35-0 82911-69-1
     Fmoc-glycine
                    33662-26-9
                                    120791-76-6 129223-22-9
                                                               166108-71-0
     106392-12-5, Poloxamer F 108
                                198139-51-4
                                              251450-64-3 283176-26-1
     167393-62-6 169543-81-1
     377087-81-5D, resin bound
                                 377087-83-7D, resin-bound 470444-40-7, BRU
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     4246-51-9P, 4,7,10-Trioxa-1,13-tridecanediamine
                                                       128988-04-5P
IT
                                                  377087-57-5P
                                                                 377087-58-6P
     150525-42-1P
                    377087-49-5P
                                   377087-50-8P
                                   377087-62-2P
                    377087-60-0P
                                                  377087-64-4P
                                                                  377087-65-5P
     377087-59-7P
                                   377087-69-9P
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     377087-66-6P
                    377087-67-7P
                                                                 377087-77-9P
                                   377087-74-6P
                                                  377087-76-8P
     377087-72-4P
                    377087-73-5P
                    377087-79-1P
                                   377087-80-4P
                                                  377088-94-3P
                                                                  468726-65-0P
     377087-78-0P
                                                  468726-71-8P
                                                                  468726-73-0P
     468726-66-1P
                   468726-68-3P
                                   468726-70-7P
                                  468726-77-4DP, resin-bound 468729-73-9P
     468726-75-2DP, resin bound
                                  470463-87-7P
                                                  470463-88-8P
                    468729-78-4P
     468729-75-1P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
IT
     41961-58-4P
     RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);
     USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting cells
        expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     10098-91-6, Yttrium 90, biological studies
                                                 13967-64-1, Dysprosium 165,
IT
     biological studies 13967-65-2, Holmium 166, biological studies
     13968-53-1, Ruthenium 103, biological studies 13981-25-4, Copper 64,
                         13982-36-0, Yttrium 88, biological studies
     biological studies
     14119-09-6, Gallium 67, biological studies
                                                 14265-75-9, Lutetium 177,
                         14378-26-8, Rhenium 188, biological studies
     biological studies
     14913-89-4, biological studies 14998-63-1, Rhenium 186, biological studies 15750-15-9, Indium 111, biological studies 15757-14-9, Gallium
     68, biological studies 15758-35-7, Ruthenium 97, biological studies
     15766-00-4, Samarium 153, biological studies
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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (preparation of radiolabeled peptide-containing compds. and compns. for
         targeting cells expressing neuropilin-1 receptor for diagnosis,
         imaging, and therapy)
IT
     42074-68-0
                   468726-76-3
     RL: RCT (Reactant); RACT (Reactant or reagent)
         (resin-bound; preparation of peptide-containing compds. and compns. for
         targeting cells expressing neuropilin-1 receptor for diagnosis,
         imaging, and therapy)
IT
     468726-69-4P
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
         (preparation of peptide-containing compds. and compns. for targeting cells
         expressing neuropilin-1 receptor for diagnosis, imaging, and therapy)
     ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
L7
     2001:885834 HCAPLUS
AN
     136:25104
DN
     Entered STN: 07 Dec 2001
ED
     Peptide-containing compounds for targeting endothelial cells, compositions
ΤI
     containing the same and methods for their use
     Von Wronski, Mathew A.; Marinelli, Edmund R.; Nunn, Adrian D.; Pillai,
     Radhakrishna; Ramalingam, Kondareddiar; Tweedle, Michael F.; Linder,
     Karen; Nanjappan, Palaniappa; Raju, Natarajan
     Bracco Research USA, USA
PA
     PCT Int. Appl., 146 pp.
SO
     CODEN: PIXXD2
DT
     Patent
LA
     English
IC
     ICM A61K051-00
CC
      63-6 (Pharmaceuticals)
     Section cross-reference(s): 1, 8, 9, 34, 35
FAN.CNT 2
                                                  APPLICATION NO.
                                                                             DATE
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     PATENT NO.
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                                                                             20010604
     WO 2001091805
                             A2
                                    20011206
                                                  WO 2001-US18053
PΤ
                                    20020906
                             A3
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              CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
              VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
          RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
                                                  CA 2001-2410887
     CA 2410887
                             AA
                                    20011206
                                                  EP 2001-944270
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     EP 1289565
                             A2
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                             T2
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                                                  JP 2001-587817
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      JP 2004500854
                              A2
                                    20000602
PRAI US 2000-585364
      WO 2001-US18053
                              W
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CLASS
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 WO 2001091805
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                           A61K047/48R2; A61K049/00P8; A61K049/22P4; A61K049/22P8;
 WO 2001091805
                   ECLA
                           A61K049/22P16; A61K051/08Z
                   FTERM 4B024/AA01; 4B024/AA20; 4B024/CA02; 4B024/DA02;
 JP 2004500854
                           4B024/DA03; 4B024/GA11; 4B024/HA17; 4B063/QA05;
                           4B063/QQ21; 4B063/QQ41; 4B063/QQ61; 4B063/QQ89;
4B063/QQ91; 4B063/QR51; 4B063/QR59; 4B063/QR77;
4B063/QS31; 4B063/QS36; 4B063/QS39; 4B063/QX01;
                            4B063/QX10; 4B065/AA90X; 4B065/AA93X; 4B065/AB01;
                            4B065/AB10; 4B065/AC14; 4B065/BA02; 4B065/BA30;
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MARPAT 136:25104

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peptide

Artery

Imaging agents

therapy)

Endothelium

therapy)

therapy) Antitumor agents

therapy)

therapy)

Angiogenesis

Diagnosis Diagnosis

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4B065/CA24; 4B065/CA43; 4B065/CA44; 4B065/CA46;
                    4C076/CC27; 4C076/DD41; 4C076/DD44; 4C076/DD45;
                    4C076/DD46; 4C076/DD51; 4C076/DD52; 4C076/DD59;
                    4C076/DD63; 4C076/DD68; 4C076/DD69; 4C076/DD70;
                    4C076/EE06; 4C076/EE30; 4C076/EE59; 4C084/AA02;
                    4C084/AA12; 4C084/BA17; 4C084/BA18; 4C084/BA42; 4C084/DA03; 4C084/NA14; 4C084/ZB26; 4H045/AA10;
                    4H045/AA20; 4H045/BA13; 4H045/BA50; 4H045/BA55;
                    4H045/EA20; 4H045/EA50; 4H045/FA31; 4H045/FA41;
                    4H045/FA50; 4H045/FA58
The present invention provides compds. for targeting endothelial cells,
tumor cells or other cells that express the neuropilin-1 (NP-1) receptor,
compns. containing the same and methods for their use. The compds. are of the
formula A-L-B (A = TKPPR or analog which specifically binds to an
endothelial cell or cells that express markers in common with endothelial
cells, with equal or greater avidity as TKPPR; L = a lipid or a non-lipid
(polymer) linker; B = a substrate). Addnl., the present invention includes diagnostic, therapeutic and radiotherapeutic compns. useful for
visualization, therapy or radiotherapy. For example, DPPE-glutaroyl-Gly-
Thr-Lys-Pro-Pro-Arq-OH (DPPE-Glu-GTKPPR) was prepared and formulated into
gas-filled microbubble compns. for ultrasonic echog. The bubbles interact
with a VEGF receptor on human aortic endothelial cells (HAEC), possibly
with KDR receptor, or more likely with NP-1 receptor which binds to KDR.
peptide neuropilin receptor endothelium targeting diagnosis therapy;
antitumor angiogenesis inhibitor peptide deriv prepn; gene therapy
radiotherapy peptide deriv; ultrasound imaging endothelium neuropilin
   (acoustic imaging contrast agents; preparation of peptide-containing compds. and
   compns. for targeting endothelial cells expressing neuropilin-1
   receptor for diagnosis and therapy)
   (acoustic; preparation of peptide-containing compds. and compns. for targeting
   endothelial cells expressing neuropilin-1 receptor for diagnosis and
   (aorta, endothelium; preparation of peptide-containing compds. and compns. for
   targeting endothelial cells expressing neuropilin-1 receptor for
   diagnosis and therapy)
   (aortic; preparation of peptide-containing compds. and compns. for targeting
   endothelial cells expressing neuropilin-1 receptor for diagnosis and
Drug delivery systems
   (beads; preparation of peptide-containing compds. and compns. for targeting
   endothelial cells expressing neuropilin-1 receptor for diagnosis and
   (cancer; preparation of peptide-containing compds. and compns. for targeting
   endothelial cells expressing neuropilin-1 receptor for diagnosis and
   (carcinoma, epidermoid; preparation of peptide-containing compds. and compns.
   for targeting endothelial cells expressing neuropilin-1 receptor for
   diagnosis and therapy)
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
   (derivs.; preparation of peptide-containing compds. and compns. for targeting
   endothelial cells expressing neuropilin-1 receptor for diagnosis and
   (detection; preparation of peptide-containing compds. and compns. for targeting
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endothelial cells expressing neuropilin-1 receptor for diagnosis and

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IT
     Diglycerides
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (digalactosyl; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
IT
     Cell activation
        (endothelial; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
ΙT
     Blood vessel
     Blood vessel
        (endothelium; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
     Fatty acids, biological studies
IT
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (esters, with lipids; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
TΤ
     Sterols
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (esters, with sugar acids; preparation of peptide-containing compds. and compns.
        for targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
ΙT
     Lipids, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (ether-linked, with fatty acids; preparation of peptide-containing compds. and
        compns. for targeting endothelial cells expressing neuropilin-1
        receptor for diagnosis and therapy)
     Vascular endothelial growth factor receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (interaction with; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
IT
     Drug delivery systems
        (liposomes; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
        therapy)
     Alcohols, biological studies
IT
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (long-chain; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
        therapy)
     Fluorescent substances
ΙT
        (markers; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
        therapy)
     Radionuclides, biological studies
IT.
     RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);
     USES (Uses)
        (markers; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
        therapy)
     Drug delivery systems
IT
        (microbubbles, gas-filled; preparation of peptide-containing compds. and compns.
        for targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
IT
     Drug delivery systems
        (microspheres; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
ΙT
     Liposomes
     Surfactants
        (nonionic; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
        therapy)
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Page 13

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IT
     Peptides, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (oligopeptides; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
TT
     Phosphoproteins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (phosphotyrosine-containing, phosphorylation; preparation of peptide-containing
        compds. and compns. for targeting endothelial cells expressing
        neuropilin-1 receptor for diagnosis and therapy)
ΙT
     Air
     Angiogenesis inhibitors
     Animal
     Antitumor agents
     Diagnosis
     Drug delivery systems
     Drug delivery systems
     Gene therapy
     Genetic vectors
     Human
     Imaging
     Imaging agents
     Radiopharmaceuticals
     Radiotherapy
     Reducing agents
     Retroviral vectors
     Sound and Ultrasound
     Viral vectors
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
ΙT
     Alkenes, biological studies
     Alkynes
     Cardiolipins
     Ceramides
     Fatty acids, biological studies
     Glycolipids
     Glycosphingolipids
     Hydrocarbons, biological studies
     Lipids, biological studies
     Lipopolysaccharides
     Lysophospholipids
     Nucleic acids
     Perfluorocarbons
     Perfluorocarbons
     Phosphatidic acids
     Phosphatidylinositols
     Phospholipids, biological studies
     Polymers, biological studies
     Saponins
     Sphingolipids
     Sulfatides
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
     Phosphorylation, biological
ΙT
        (protein, protein tyrosines; preparation of peptide-containing compds. and
        compns. for targeting endothelial cells expressing neuropilin-1
        receptor for diagnosis and therapy)
     Carbohydrates, biological studies
ΙT
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (sugar esters, with aliphatic acids; preparation of peptide-containing compds. and
        compns. for targeting endothelial cells expressing neuropilin-1
        receptor for diagnosis and therapy)
IT
     Drug delivery systems
        (suspensions; preparation of peptide-containing compds. and compns. for
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targeting endothelial cells expressing neuropilin-1 receptor for

```
diagnosis and therapy)
    Vascular endothelial growth factor receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (type VEGFR-2, interaction with; preparation of peptide-containing compds. and
        compns. for targeting endothelial cells expressing neuropilin-1
        receptor for diagnosis and therapy)
     Endothelium
TТ
     Endothelium
        (vascular; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
IT
     127464-60-2, Vascular endothelial growth factor
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (binding to neuropilin-1 and KDR receptors; preparation of peptide-containing
        compds. and compns. for targeting endothelial cells expressing
        neuropilin-1 receptor for diagnosis and therapy)
     14133-76-7DP, Technetium 99, complexes with tetrapeptide conjugate,
TT
     biological studies
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (metastable; preparation of peptide-containing compds. and compns. for targeting
        endothelial cells expressing neuropilin-1 receptor for diagnosis and
        therapy)
                                                        56-40-6, Glycine,
     56-12-2, γ-Aminobutyric acid, biological studies
IT
     biological studies 56-84-8, L-Aspartic acid, biological studies
     56-86-0, L-Glutamic acid, biological studies
                                                     1197-18-8,
     trans-4-Aminomethylcyclohexanecarboxylic acid
                                                    9063-57-4, Tuftsin
     214210-47-6, Neuropilin-1
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
     41961-58-4DP, conjugates with red fluorescent carboxylate-modified
IT
                145018-54-8DP, FluoSphere, red fluorescent
     carboxylate-modified, conjugates with peptide
     RL: BSU (Biological study, unclassified); DGN (Diagnostic use); SPN
     (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);
     PREP (Preparation); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
IT
     41961-58-4P
     RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic
     preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant
     or reagent)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
                    377087-53-1P
                                   377087-54-2P
                                                  377087-63-3P
IT
     377087-37-1P
                                   377088-93-2P
                                                                  377725-30-9P
                                                  377725-24-1P
                    377088-92-1P
     377087-82-6P
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     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
     56-87-1, L-Lysine, reactions 72-19-5, L-Threonine, reactions Glutaric anhydride 1155-64-2 1663-39-4, tert-Butyl acrylate
                                                                       108-55-4,
IT
                                                                    15401-08-8
                             7672-27-7
     2149-70-4 4530-20-5
                                        15260-10-3
                                                      15401-08-8
                                           129223-22-9 135821-02-2
                  71989-26-9
                              71989-35-0
     29022-11-5
                                                195136-58-4
                                                              377087-58-6
                   167393-62-6
                                 169543-81-1
     166108-71-0
                   377087-81-5
                                  377087-84-8
     377087-61-1
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
                                   377087-43-9P
                                                   377087-44-0P
                                                                  377087-45-1P
IT '
                    198139-51-4P
     128988-04-5P
                                                                  377087-50-8P
     377087-46-2P
                    377087-47-3P
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                    377087-72-4P
     377087-71-3P
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     377088-94-3P
                   377725-26-3P
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     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
                5681-36-7, Dipalmitoylphosphatidylethanolamine
                                                                  106392-12-5,
IT
     Ethylene oxide-propylene oxide block copolymer
     RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT
     (Reactant or reagent); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
     56-81-5, Glycerol, biological studies 56-81-5D, Glycerol, esters
IT
     57-88-5, Cholesterol, biological studies 110-15-6, Succinic acid,
     biological studies 110-94-1, Glutaric acid 124-30-1, Stearylamine
     124-38-9, Carbon dioxide, biological studies 141-82-2, Malonic acid,
     biological studies 144-62-7, Oxalic acid, biological studies 538-24-9,
                         1256-86-6, Cholesterol sulfate 1510-21-0,
     Glycerol trilaurate
     Cholesterol hemisuccinate 2197-63-9, Dicetyl phosphate 2551-62-4,
     Sulfur hexafluoride 3614-36-6, Diacetyl phosphate 4345-03-3
     4537-76-2, Distearoylphosphatidylethanolamine 7439-90-9, Krypton,
     biological studies
                          7440-37-1, Argon, biological studies
     Xenon, biological studies 7727-37-9, Nitrogen, biological studies
     7782-44-7, Oxygen, biological studies 9002-89-5, Polyvinyl alcohol
     9004-54-0D, Dextran, derivs. 10098-91-6, Yttrium-90, biological studies
    13967-64-1, Dysprosium-165, biological studies 13967-65-2, Holmium-166, biological studies 13968-53-1, Ruthenium-103, biological studies
     13981-25-4, Copper-64, biological studies 13982-36-0, Yttrium-88,
     biological studies 14119-09-6, Gallium-67, biological studies
     14133-76-7, Technetium-99, biological studies
                                                     14265-75-9, Lutetium-177,
     biological studies 14378-26-8, Rhenium-188, biological studies
     14913-89-4, biological studies 14998-63-1, Rhenium-186, biological
                                                           15757-14-9,
              15750-15-9, Indium-111, biological studies
     Gallium-68, biological studies 15758-35-7, Ruthenium-97, biological
             15766-00-4, Samarium-153, biological studies 20255-95-2,
     Dimyristoylphosphatidylethanolamine 24529-88-2 25322-68-3D,
     Polyethylene glycol, derivs. 26657-95-4, Glycerol dipalmitate
     27638-00-2, Glycerol dilaurate 55252-82-9
                                                  68354-92-7
     76822-97-4 78543-25-6, 1-Hexadecyl-2-palmitoylglycerophosphoethanolamine
                 87136-19-4
                             108032-13-9
                                            161293-59-0
                                                           161441-83-4
     83554-62-5
     186198-32-3
                 377088-91-0
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
                                                      377087-83-7
     4246-51-9, 4,7,10-Trioxa-1,13-tridecanediamine
IT
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (support-bound; preparation of peptide-containing compds. and compns. for
        targeting endothelial cells expressing neuropilin-1 receptor for
        diagnosis and therapy)
     377087-37-1P
     RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic
     use); BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of peptide-containing compds. and compns. for targeting endothelial
        cells expressing neuropilin-1 receptor for diagnosis and therapy)
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AN.S DCR-741583
DCSE 741583-1-0-0
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *
CMT Gly-Thr-Lys-Pro-Pro-Arg 1 N-dipalmitoylphophatidylethanolamine-glutaroyl
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MF
=> d all dcn l14 tot
L14 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
     2003-800817 [75]
AN
                        WPIX
     2002-195523 [25]
CR
DNC C2003-221021
     Composition used in targeting endothelial cells e.g. tumor cells comprises
     compounds containing monomers, multimers or polymers of
     L-arginine-L-threonyl-L-lysyl-L-prolyl-L-prolyl.
DC
     LINDER, K; MARINELLI, E R; NANJAPPAN, P; NUNN, A D; PILLAI, R; RAJU, N;
     RAMALINGAM, K; TWEEDLE, M F; VON WRONSKI, M A
     (LIND-I) LINDER K; (MARI-I) MARINELLI E R; (NANJ-I) NANJAPPAN P; (NUNN-I) NUNN A D; (PILL-I) PILLAI R; (RAJU-I) RAJU N; (RAMA-I) RAMALINGAM K;
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     US 2002147136 A1 20021010 (200375)*
                                                 85
                                                       A61K038-16
PΙ
ADT US 2002147136 A1 CIP of US 2000-585364 20000602, US 2001-871974 20010604
                                                           20000602
                           20010604; US 2000-585364
PRAI US 2001-871974
     ICM A61K038-16
IC
     ICS A61K051-08
     US2002147136 A UPAB: 20031120
     NOVELTY - Composition (A1) comprises compounds containing monomers,
     multimers or polymers of L-arginine-L-threonyl-L-lysyl-L-prolyl-L-prolyl.
          DETAILED DESCRIPTION - Composition (A1) comprises a compound
     containing monomers, multimers or polymers of L-arginine-L-threonyl-L-
     lysyl-L-prolyl-L-prolyl (TKPPR) of formula A-L-B1 (I).
          A = monomer, multimer or polymer of TKPPR or its analogue that
     specifically binds to NP-1 or cells that express NP-1 with avidity of at
     least that of TKPPR;
          L = a linker (preferably a group of formula (i));
          X = NH, NR, O, S or SR;
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m = 0-2;
n = 0-4;
     R = H or 1-4C alkyl (optionally substituted by at least one OH), and
     B1 = a substrate.
     INDEPENDENT CLAIMS are also included for:
     (1) a compound of formula A-L-B1a (II) and A-L-B3 (III) for use in
targeting endothelial cells, tumor cells or other cells;
     (2) an ultrasound contrast agent (c1) comprising a suspension of gas
filled microbubbles comprising (II);
     (3) an ultrasound contrast agent (c2) comprising a suspension of gas
filled microballoons comprising (III);
     (4) preparation of (I) which comprises conjugating the monomer,
multimer or polymer of TKPRR or its analogue with a linker to obtain a
compound of formula A-L (IV), forming a covalent or non-covalent bond
between (IV) and the substrate B1 or forming a covalent bond between B1
and the linker to form a conjugate B-L followed by conjugation with the
monomer, and
     (5) a kit for preparing a radiopharmaceutical comprising (A1).
     Bla = a phospholipid group of formula (ii);
     M = alkaline or alkaline earth metal cation;
     R1, R2 = 12-20C linear chain optionally interrupted by CO or O, and
     X2 = H, CH2CH2NH2, CH2CH(NH3+)-COO-, CH2CH(OH)CH2OH or a group of
formula (iii).
     ACTIVITY - Cytostatic; Antiangiogenetic.
     MECHANISM OF ACTION - Vascular endothelial growth factor binding
receptor transmembrane glycoprotein (NP-1) binder.
     USE - Used for targeting endothelial cells, tumor cells or other
cells which express NP-1, for inhibiting angiogenesis, for ultrasound
imaging, staging a tumor, screening at least one targeted ultrasound
contrast agent for the ability to target endothelial cells, tumor cells or
other cells which express NP-1, for the therapeutic delivery in vivo of a
bioactive agent and for delivering desired nucleic acids to endothelial
cells, tumor cells or other cells which express NP-1 (all claimed). The
composition is also useful for visualization therapy or radiotherapy of
endothelial cells.
     ADVANTAGE - (A1) can be used with or without a detectable moiety for
any of the imaging modalities.
Dwg.0/4
CPI
AB; GI; DCN
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     B04-C03; B04-D01; B04-J02; B05-A03B; B05-A04; B05-B01P; B05-B02C;
     B05-C08; B10-A07; B10-B02J; B10-B04B; B10-C02; B10-H02B; B12-K04C1;
     B14-F01D; B14-H01; K08-X; K09-B; K09-E
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FS

FA

MC

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